THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

AUG 26 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99D-0529
Draft Guidance for Industry on Changes to an Approved NDA or ANDA

Dear Sir/Madam:

Reference is made to the above-noted Draft Guidance originally published in the Federal Register on 28 June 1999, Docket Number 99D-0529.

At this time, on behalf of The R.W. Johnson Pharmaceutical Research Institute (RWJPRI), we wish to provide our comments to this Draft Guidance. Our comments are both General and specific and are identified as such.

We greatly appreciate the opportunity to comment on this document and look forward to similar opportunities in the future.

Very truly yours,

Donna Panasewicz
Director
Regulatory Affairs

Attachment

99D-0529

C 34

General Comments
We concur with PhRMA's and PDA's recommendation that the term "validate," used throughout the document, should be revised to "assess," "evaluate" or "confirm," to avoid potential confusion with the cGMP definition of "validation," which would not apply here.

We also concur with PhRMA's opinion regarding the fact that the proposed changes do not meet the intent of congress and FDAMA regarding the fact that what was being hoped to be achieved was the reduction in prior approval supplements and reporting requirements which in fact will not be met by this guidance.

We also urge the Agency to commit to minimize the time period between issuance of the final guidance document and corresponding revisions to the SUPAC guidelines, to avoid inconsistencies between the documents.

We recommend that the term successful cGMP inspection be further defined to include a time period since the inspection occurred, i.e. within two years of submission.

We respectfully request that the Agency consider some sort of "Grandfathering" of changes which are already in progress by industry based upon already approved SUPAC guidances. There are many cases where regulatory filing strategies have already been implemented internally in industry and now with the change to 314.70 the reporting requirements have changed , ie from a CBE 30 to a PAS, or there was no requirement in the current 314.70 and now one exists. Our ability to continue to supply product to the marketplace can be adversely impacted by now having to redefine the reporting requirements and extend the time to implementation.

Line 56 - "extraordinary hardship" and expedited review
As discussed at the FDA/Industry meeting, please consider adding mandatory vendor-imposed changes (without sufficient reaction time) to the list of "not reasonably foreseen" events.

Line 82, 778, 782 - comparability protocols
As discussed at the FDA/Industry meeting, we urge the Agency to consider a CBE-30, rather than PAS filing mechanism for these protocols, based on their expected brevity for review. Also, we support the position that such protocols should be fileable for approval in *original* NDAs, in addition to post-approval filings. We would like to operate with the understanding that, if a relevant protocol is subsequently published in an official compendia or Agency document (guidance, et al), the less burdensome protocol may be applied. Finally, we would welcome the Agency's involvement in drafting "common" comparability protocols, so consistent requirements are imposed on all sponsors. Alternatively, Agency guidance on comparability protocol format/content would be helpful.

Line 89 - listing all CMC changes in the supplement/annual report cover letter
We recommend that this requirement be more flexible. In order to avoid a lengthly cover letter we recommend that the items be only bulleted and not in as much detail as is contained in the actual CM&C section. To repeat verbatum what is contained in the CM&C section would be redundant.

Line 90-96 - cGMP obligations
It is our opinion that this paragraph should not be included in the guidance, as it is part of general GMP regulations - not 21 CFR 314.70. We definitely agree that cGMP's should be followed, however it is not necessary to state this in this guidance.

Line 187 - changes in quantitative composition, including inactive ingredients
We note that the quantitative levels of inactive ingredients are covered in certain SUPAC guidances and list percentage ranges over which the components can be varied. For example, a change of up to 5% in an excipient is considered a minor change in SUPAC-SS and may be reported in the Annual Report. This guidance should follow the standards set by SUPAC in this regard.

Line 213 – (2) the type of operation used to be performed but at some time had been discontinued and is now being restarted
We request that this sentence be modified to include a specific time frame from discontinuation to restart as well as the term " type of operation" be further defined.

Line 215 - (3) the facility does not have a satisfactory CGMP inspection.
The sentence is footnoted , which then references the glossary. We suggest that the definition be included in the sentence.

Line 285 - site change for DS manufacture, with unchanged process and satisfactory cGMP
Under current 21 CFR 314.70(c)(3), such a change is listed as CBE. Under the draft guidance where this type of change would be a CBE in 30 days represents and increase in the required reporting requirements which is in conflict with the intent of FDAMA.

Line 324 – Site changes within a single facility (e.g. room changes).
We wish to note that historically floor plans have not been submitted for NDA's for drugs. To now have to report a room change is a more stringent reporting requirement which is not the intent of FDAMA. In addition, to now be required to note a room change would mean nothing to the Agency reviewer as they would not have anything to compare the room change to.

Line 333 - change in floor plan
This information is not typically part of the NDA filing, but subject to Field inspection.

Line 335 - manufacturing area improvements
This example is vague and subject to misinterpretation. We also wish to note that it is our opinion that industry should be able to make improvements to the facility to provide greater assurance of quality without having to report these changes, the exception of course would be for parenteral facilities. To have to report upgrades to facilities for all other dosage forms would be imposing a more stringent requirement than currently exists.

Line 357, 370 - "changes may affect product sterility assurance"
As discussed at the FDA/Industry meeting, we suggest clarifying that these are changes with "potential *negative* (or adverse) impact on sterility."

Line 374 - PAS for addition, deletion or substitution of aseptic processing steps
Addition or substitution of aseptic processing steps may not negatively impact sterility assurance, and in fact could enhance sterility assurance. In these cases, PAS would not be warranted.

Line 401 - PAS for filter size/material changes
Consider that these changes may be CBE-30, based on accumulation and submission of appropriate comparability data to existing filter.

Line 413 – Filtration to centrifugation or vise versa
This item should be listed under item number 5, line 415 due to the fact that it is pertinent to drug substance.

Line 414 - PAS for DS synthesis change
Changes in DS synthesis route, which occur prior to the formation of key intermediates, should not be regarded as major changes, since the potential to impact the quality, strength, identity and purity of the final product is low. In addition, this item should be listed under item number 5, line 415 due to the fact that it is pertinent to drug substance.

Line 423 - PAS for inks not currently used in CDER-approved products
Is there is list of all CDER-approved inks?

Line 494- 495 – All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance(21CFR 314.70(b)(2)(I).
We suggest that the sentence be restructered as follows: All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by ***regulation (21CFR 314.70(b)(2)(I) or guidance.***

Line 540-556 - CBE-30 for relaxing acceptance criteria or deleting a test for raw materials, starting materials or intermediates used in DS synthesis; changed analytical procedure
Under the draft BACPAC I guidance, relaxing an acceptance criteria is considered a CBE supplement. A change to CBE-30 represents an increased reporting requirement over the existing guidance. Also, if the change is to comply with an official compendium, it should be filed in an annual report.

Line 567 - AR for change to comply with official compendium if consistent with FDA requirements and provides same or greater level of assurance....
The criteria that the change be "consistent with FDA requirements" and "provide the same or greater level of assurance" represents an increased regulatory burden over the existing 21 CFR 314.70(d)(1). In addition, it dilutes the status of the USP/NF as official US compendia. It has the potential to produce inconsistent standards for the same drug, depending on source. Finally, it can impose a competitive disadvantage to innovator firms who must comply with USP and (possibly more stringent) FDA requirements, while generic equivalents may conform only with USP.

Line 584, 794-799 - tightening specifications for reference standards
Under existing CDER Guidance Documents (Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Feb. 1987), there is no requirement for specifications for reference standards. This section of the proposed rule represents implementation of such a requirement and therefore represents an increased reporting requirement.

Line 619 - PAS for change to ink/adhesive that has not been approved by CDER
Is there is list of all CDER-approved inks and adhesives, with corresponding packaging components for which they are used?

Line 647 - CBE-30 for change in secondary packaging components, not otherwise listed
Secondary packaging components, not intended to provide additional DP protection, are typically not described in the NDA. As such, they should not be subject to this filing requirement.

Line 677-682 and 693-694 - AR for change/addition of cap liner or seal; change in antioxidant, stabilizer or mold releasing agent
We thank the Agency for this clarification and regulatory relief.

Line 695-700 - AR for change to blister package that provides same or better protective properties, if CDER-approved for same type product
We thank the Agency for this clarification and regulatory relief.

Line 711-713 - AR for change in secondary packaging components, not intended to provide additional protection to the DP
Secondary packaging components, not intended to provide additional DP protection, are typically not described in the NDA. As such, they should not be subject to this filing requirement.

Line 717-718 - "applicant must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations...."
We respectfully request clarification of the term "prompt." For changes which do not affect the safe use of the product, we suggest "prompt" be defined as a period for revision implementation of six months to one year. Changes which could affect safe use of the product should be implemented more rapidly.

Line 736 – Change in labeled storage conditions, unless exempted by regulation or guidance
This statement is unclear and would imply that if you changed the label to comply with the current USP definition a PAS would be required. For older products,if you currently had store at room temperature and now are defining room temperature by USP you would have to submit a PAS.

Line 776-777 - PAS for "changes that may affect product sterility assurance"
As stated above, we suggest that this be clarified to "changes which may *negatively* (or adversely) impact sterility assurance."

Line 793 - 2. Addition of time points to the stability protocol
We request that this sentence be modified to state **the permanent** addition of additional stability time points. Industry may elect to test a given lot at additional time points for various reasons and they way the sentence is written could be misinterpreted that in these instances it would need to be reported to the annual report.

Line 795 – Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application
We request that it be defined as to whether this is referring to compendial or non-compendial reference standards. It is our opinion that if every company has to report these type of changes the Agency will be deluged with these notifications which really add no value to the reviewer. This is an area which can be reviewed by the Agency Field Inspectors in routine cGMP inspections. We also wish to note that this requirement is more stringent than currently exists for drugs and thus is an increased reporting requirement.

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R W JOHNSON PRI
920 ROUTE 202 SOUTH
RARITAN NJ 08869
(908)704-4781

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